COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING COMPLEX REGIONAL PAIN SYNDROME

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/279,232, filed May 15, 2014, which is a continuation of U.S. patent application Ser. No. 14/063,979, filed Oct. 25, 2013, which is a continuation-in-part of U.S. patent application Ser. No. 13/894,274, filed May 14, 2013, which embodiments the benefit of U.S. Provisional Applications 61/646,538, filed May 14, 2012; 61/647,478, filed May 15, 2012; 61/654,292, filed Jun. 1, 2012; 61/654,383, filed Jun. 1, 2012; 61/655,527, filed Jun. 5, 2012; 61/655,541, filed Jun. 5, 2012; 61/764,563, filed Feb. 14, 2013; 61/762,225, filed Feb. 7, 2013; 61/767,647, filed Feb. 21, 2013; 61/767,676, filed Feb. 21, 2013; and 61/803,721, filed Mar. 20, 2013, all of which are incorporated by reference in their entirety herein.

BACKGROUND

Bisphosphonate compounds are potent inhibitors of osteoclast activity, and are used clinically to treat bone-related conditions such as osteoporosis and Paget's disease of bone; and cancer-related conditions including multiple myeloma, and bone metastases from solid tumors. They generally have low oral bioavailability.

SUMMARY

It has been discovered that oral dosage forms of bisphosphonate compounds, such as zoledronic acid, can be used to treat or alleviate pain or related conditions.

Some embodiments include a method of enhancing the oral bioavailability of zoledronic acid comprising orally administering a dosage form containing zoledronic acid in the disodium salt form.

Some embodiments include a dosage form comprising zoledronic acid in the disodium salt form, wherein the bioavailability, in a mammal, of zoledronic acid in the disodium salt form is greater than the bioavailability of zoledronic acid in the diacid form would be in the same dosage form.

Some embodiments include a dosage form comprising zoledronic acid in the disodium salt form, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that provides an area under the plasma concentration curve of zoledronic acid of about 4 ng·h/mL to about 2000 ng·h/mL to a human being to which the dosage form is administered.

Some embodiments include a dosage form comprising zoledronic acid in the disodium salt form, wherein the disodium salt form is present in a lower molar amount than would be present if the zoledronic acid were in the diacid form; and wherein the zoledronic acid in the disodium salt form has an improved bioavailability as compared to the zoledronic acid in the diacid form to the extent that the lower molar amount of the disodium salt in the dosage form does not reduce the amount of zoledronic acid delivered to the plasma of a mammal.

Although an oral dosage form with enhanced bioavailability with respect to the bisphosphonate compound can be used, the treatment can also be effective using an oral dosage form that includes a bisphosphonate compound, such as zoledronic acid, wherein the bioavailability of the bisphosphonate is unenhanced, or is substantially unenhanced.

Some embodiments include a method of relieving inflammatory pain comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof, wherein the mammal experiences significant pain relief more than 3 hours after administration of the dosage form.

Some embodiments include a method of relieving pain associated with an arthritis comprising administering an oral dosage form containing zoledronic acid to a human being in need thereof.

Some embodiments include a method of treating complex regional pain syndrome comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof.

Some embodiments include an oral dosage form comprising zoledronic acid, wherein the oral bioavailability of zoledronic acid is substantially unenhanced. For example, in some embodiments, the oral bioavailability in the dosage form is about 0.01% to about 4%.

Some embodiments include a pharmaceutical product comprising more than one unit of an oral dosage form described herein. In some embodiments, each unit of the oral dosage form contains about 1 mg to about 50 mg of zoledronic acid.

Some embodiments include a method of relieving inflammatory pain comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof.

In some embodiments, the mammal receives a total monthly dose of zoledronic acid that is about 800 mg/m^2 or less.

In some embodiments, the dosage form contains about 10 mg/m^2 to about 20 mg/m^2 based upon the body surface area of the mammal.

Some embodiments include a method of relieving inflammatory pain comprising orally administering zoledronic acid to a mammal in need thereof.

In some embodiments, about 300 mg/m^2 to about 600 mg/m^2 of zoledronic acid is administered per month, based upon the body surface area of the mammal.

In some embodiments, about 50 mg/m^2 to about 600 mg/m^2 of zoledronic acid is administered per month, based upon the body surface area of the mammal.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** is a plot of pain compression thresholds in a rat model of inflammatory pain using three different doses of zoledronic acid. Measurements were taken at baseline (BL) and at various time points after dosing on the days indicated.

FIG. **2**A is a graph depicting reversal of arthritis pain for two different doses of zoledronic acid in a rat model of arthritis pain.

FIG. **2**B is a graph depicting pain thresholds for two different doses of zoledronic acid in a rat model of arthritis pain.

FIG. **3** is a graph summarizing the results for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

FIG. **4** depicts hindpaw pain thresholds for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

FIG. **5** depicts weight bearing for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

FIG. **6** depicts paw thickness change for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.